

Applicant : George F. Vande Woude et al.
Appln. No. : 10/563,616
Page : 7

REMARKS

The Office Action dated January 21, 2010, includes a requirement for a group election and species election. Based on the provisional election the Examiner believed Applicants had made, claims 1, 5, 7, 8, 11, 12, 20, and 21 were considered, but were rejected under 35 U.S.C. §§ 102(e), 103, and 112. As set forth below, there was a miscommunication regarding the claims Applicants had elected. Accordingly, claims 8 and 29 have been amended; claims 1, 5, 7-13, 16-18, 20, 21, 30, 31, 34, 37, 38, 40-42 have been withdrawn; and claims 22, 26, 28, 29, 32, 33, and 43-46 are pending.

Election/Restrictions

In the Office Action, restriction was required under 35 U.S.C. 121 and 372. The Applicants were required to elect between Group I and Group II claims. Group I is drawn to a method of inhibiting tumor angiogenesis comprising providing to cells that undergo angiogenesis or participate in angiogenesis, an effective amount or amounts of (a) one or more of thrombospondin-1 (TSP-1), an antiangiogenic derivative thereof, or a TSP-1 agonist or mimic; and in combination with (b) one or more inhibitors of the action or expression of (i) HGF/SF receptor Met, (ii) VEGF or the VEGF receptor; and (iii) both (i) and (ii), thereby inhibiting said angiogenesis. Group II is drawn to a composition comprising (a) one or more of TSP-1, an antiangiogenic derivative thereof, or a TSP-1 agonist or mimic; and in combination with (b) one or more inhibitors of the action or expression of (i) HGF/SF receptor Met, (ii) VEGF or the VEGF receptor; and (iii) both (i) and (ii).

The Office Action indicates as follows: Groups I and II do not relate to a single inventive concept under PCT Rules 13.1 and 13.2 because the technical feature linking Groups I and II

Applicant : George F. Vande Woude et al.
Appln. No. : 10/563,616
Page : 8

appears to be TSP-1 and an inhibitor of VEGF which do not constitute a special technical feature in view of Stein et al. U.S. Patent No. 7,351,729, filed March 7, 2003, issued April 1, 2008, and claiming priority to March 8, 2002.

The Office Action indicates that, during a telephone conversation with the undersigned on January 6, 2010, a provisional election was made to prosecute the invention of Group I. However, there apparently was a misunderstanding during this telephone conversation: Applicants would like to prosecute the product claims of Group II; and, if the product claims of Group II are found allowable, rejoin the process claims of Group I. The claims readable on Group II are 22, 26, 28-34, 37, 38, and 40-46.

The Office Action also indicates that a species election is required as the species identified do not relate to a single general inventive concept under PCT Rule 13.1 and 13.2. Applicants elect the species of (a) TSP-1 or an TSP-1 agonist in combination with one or more inhibitors of the action or expression of (i) HGF/SF of the HGF/SF receptor Met, (ii) VEGF of the VEGF receptor, or (iii) both (i) and (ii) (section 4), TSP-1 or anti-angiogenic derivative (section 5), an inhibitor of VEGF (section 6), and a VEGF inhibitor anti-VEGF antibody (section 7).

Claim Rejection Under 35 U.S.C. § 112

The Office Action indicates that claim 8 does not comply with 35 U.S.C. § 112, second paragraph, because the claim identifies the trademark Avastin® (Office Action, p. 10). Applicants have amended claims 8 and 29 to recite the monoclonal antibody in the products, namely, bevacizumab.

Applicant : George F. Vande Woude et al.
Appln. No. : 10/563,616
Page : 9

Claim Rejection Under 35 U.S.C. § 102(e)

The Office Action rejected claims 1, 5, 7, 8, 11, 12, 20, and 21 over Stein et al. U.S. Patent No. 7,351,729 (“the Stein et al. patent”). As noted above, Applicants have elected to prosecute the product claims of the present application, namely, claims 22, 26, 28, 29, 32, 33, and 43-46. In expectation that the next Office Action may reject these claims over the same Stein et al. patent, and in an effort to conduct compact prosecution, Applicants respectfully submit arguments regarding the patentability of claims 22, 26, 28, 29, 32, 33, and 43-46 over the Stein et al. patent.

The Office Action indicates that Stein et al. teach a method of administering one or more angiogenesis inhibitors including anti-VEGF antibody bevacizumab and TSP-1 to treat cancer (Office Action, at p. 12). As noted, Applicants expect the next Office Action may similarly assert that the compositions of claims 22, 26, 28, 29, 32, 33, and 43-46 are anticipated by the Stein et al. patent.

The Stein et al. patent claims an effective filing date of March 8, 2002. However, Applicants herewith submit (a) a (first) Declaration Under 37 C.F.R. § 1.131 and (b) a (second) Declaration of Livnat Under 37 C.F.R. § 1.131 indicating that the inventions of claims 22, 26, 28, 29, 32, 33, and 43-46 were conceived prior to March 8, 2002, and Applicants were reasonably diligent in reducing the invention to practice from prior to March 8, 2002, until the filing of Applicants’ priority application on July 7, 2003. Also, attached to the (first) Declaration Under 37 C.F.R. § 1.131 are documents showing experiments from the laboratory notebook of Yu-Wen Zhang, one of the inventors of the present application. Because Applicants have antedated the Stein et al. patent, Applicants respectfully submit that the reference should not be

Applicant : George F. Vande Woude et al.
Appln. No. : 10/563,616
Page : 10

applied against claims 22, 26, 28, 29, 32, 33, and 43-46 of the present application and the rejection based on this reference should be withdrawn.

Further, even if the Stein et al. patent is applied as prior art, Applicants respectfully contend that the disclosure of this reference relied on in the Office Action (Col. 58, lines 16-41) does not anticipate claims 22, 26, 28, 29, 32, 33, and 43-46 of the present application. In particular, the combination claimed by Applicants (TSP-1 and a VEGF inhibitor) is not specifically named in the Stein et al. reference. Instead, the Stein et al. patent indicates that a JNK inhibitor may be combined with one or more angiogenesis inhibitors from a list of sixty-three (63) agents. First, a combination of TSP-1 and a VEGF inhibitor is not identified in the Stein et al. patent because all of the agents in the list necessarily are combined with a JNK inhibitor. Second, even if the JNK inhibitor was somehow excluded from the combination, there are so many possible composition combinations that one of ordinary skill in the art cannot “at once envisage” the specific combination of TSP-1 and a VEGF inhibitor. (See, MPEP §2131.02, third subsection). Instead, the number of possible combinations is vast. The Stein et al. disclosure can include each of the 63 agents alone, combinations of 2 agents selected from the 63 agents, combinations of 3 agents selected from the 63 agents, combinations of 4 agents selected from the 63 agents, combinations of 5 agents selected from the 63 agents, combinations of 6 agents selected from the 63 agents, etc. In total, there are 63 factorial (63!) possible combinations disclosed by Stein et al.; a vast number to be sure. Accordingly, Applicants respectfully submit claims 22, 26, 28, 29, 32, 33, and 43-46 of the present application are not anticipated by the Stein et al. patent, and the rejection based on this reference should be withdrawn.

Applicant : George F. Vande Woude et al.
Appln. No. : 10/563,616
Page : 11

Claim Rejection Under 35 U.S.C. § 103

The Office Action rejected Claims 1, 5, 7, 8, 11, 12, 20, and 21 under 35 U.S.C. §103(a) as being unpatentable over Rosen (*Cancer Control*, March/April 2002, 9:36-44) in view of Lawler US Patent 7,223,731, Streit et al. (*American J. Pathology*, 199, 155:441-452), and Burke et al. (*Critical Reviews in Oncology*, 2001, 39: 155-171). As with the §102 rejection, in expectation that the next Office Action may reject claims 22, 26, 28, 29, 32, 33, and 43-46 over this same combination of references, and in an effort to conduct compact prosecution, Applicants respectfully submit arguments regarding the patentability of claims 22, 26, 28, 29, 32, 33, and 43-46 over Rosen, in view of the Lawler '731 patent, Streit et al., and Burke et al.

The Office Action indicates Rosen teach administering an anti-VEGF antibody, and that TSP-1 is a known anti-angiogenic factor, but do not teach a combination of TSP-1 and a VEGF inhibitor; however the Lawler '731 patent and the Streit et al. reference disclose administering TSP-1 to treat cancer or to inhibit angiogenesis (Office Action, p. 13). The Office Action further states that Burke et al. (generally) disclose combining anti-angiogenic agents to produce a synergistic combination. As noted in the Office Action (p. 14), none of the references specifically teach combining together TSP-1 and a VEGF inhibitor; but the Office Action also state this combination would have logically followed from these agents having been individually taught for the same purpose (Office Action, pp. 14-15). However, as discussed above, even if we limit potential anti-angiogenic agents to the 63 identified by Stein et al., there are an unlimited number of combinations of anti-angiogenic agents that might possibly have a synergistic effect; and the majority of these agents likely target different molecular mechanisms. It is not obvious to try this combination where the prior art gives no direction as to which of many possible choices

Applicant : George F. Vande Woude et al.
Appln. No. : 10/563,616
Page : 12

is likely to be successful. *In re Kubin*, 561 F.3d 1351, 1359, 90 U.S.P.Q.2d 1417 (2009), The number of possible combinations is vast, and the effect of these combinations unpredictable. *Id.* Moreover, there is no reason for one of skill in the art to predict any one combination would have a synergistic effect. Here, the synergy identified by Applicants was further demonstrated by Filleur et al. [*Cancer Research*, 63, 3919-3922, July 15, 2003, Exhibit A hereto]. In particular, Filleur show the combination of anti-angiogenic agents produce synergistic effects (see, Filleur, p. 3922, entire Column 1).

Based upon the above, Applicants respectfully contend that it would not have been obvious for a person of ordinary skill to combine Rosen, the Lawler '731 patent, Streit et al., and Burke et al. to obtain the invention of claim 22. Because claims 26, 28, 29, 32, 33, and 43-46 depend from claim 22 and, therefore, include additional claim elements, Applicants also respectfully contend that claims 26, 28, 29, 32, 33, and 43-46 are non-obvious over the cited combination of references.

Applicants respectfully request that this Section 103 rejection be withdrawn and claims 22, 26, 28, 29, 32, 33, and 43-46 allowed.

Rejoinder of Claims

Applicants request rejoinder of the withdrawn method claims. Claims 1, 5, 7, 8, 11, 12, 20, and 21 include all of the elements of the pending product claims. Therefore, if the pending product claims are allowed, Applicants respectfully request that withdrawn claims 1, 5, 7, 8, 11, 12, 20, and 21 be rejoined with the pending claims and allowed.

Applicant : George F. Vande Woude et al.
Appln. No. : 10/563,616
Page : 13

Conclusion

If the Examining Attorney has any questions regarding this election, Applicants respectfully request that the Examining Attorney contact the undersigned at the telephone number indicated below or email the undersigned at dsiegel@priceheneveld.com.

Respectfully submitted,

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Date

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